

(19) World Intellectual Property  
Organization  
International Bureau



(43) International Publication Date  
27 January 2005 (27.01.2005)

PCT

(10) International Publication Number  
**WO 2005/007193 A3**

(51) International Patent Classification<sup>7</sup>: **A61K 38/17**,  
38/18, 38/19, 38/21, 45/00, 45/06, A61P 35/00

(21) International Application Number:  
PCT/US2004/021641

(22) International Filing Date: 7 July 2004 (07.07.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
60/484,676 7 July 2003 (07.07.2003) US

(71) Applicant: **VANDE WOUDE, George, F.** [US/US]; 9451  
Bailey Drive N.E., Ada, MI 49301 (US).

(71) Applicant and

(72) Inventor: **ZHANG, Yu-Wen** [CN/US]; 532 Briar Lane,  
N.E., Grand Rapids, MI 49503 (US).

(74) Agent: **LIVNAT, Shmuel**; Venable LLP, P.O. Box 34385,  
Washington, DC 20043-9998 (US).

(81) Designated States (unless otherwise indicated, for every  
kind of national protection available): AE, AG, AL, AM,  
AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN,  
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI,  
GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE,  
KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD,  
MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG,  
PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM,  
TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM,  
ZW.

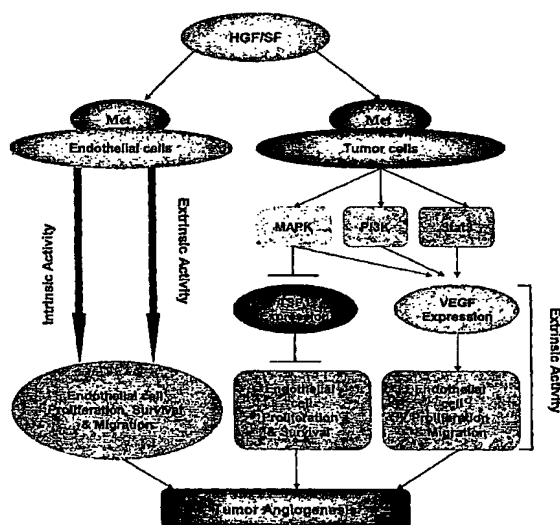
(84) Designated States (unless otherwise indicated, for every  
kind of regional protection available): ARIPO (BW, GH,  
GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM,  
ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),  
European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI,  
FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI,  
SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ,  
GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

[Continued on next page]

(54) Title: INHIBITION OF TUMOR ANGIOGENESIS BY COMBINATION OF THROMBOSPONDIN-1 AND INHIBITORS  
OF VASCULAR ENDOTHELIAL GROWTH FACTOR



(57) Abstract: Hepatocyte growth factor/scatter factor (HGF/SF), acting through the Met receptor, plays an important role in most human solid tumors and inappropriate expression of this ligand-receptor pair is often associated with poor prognosis. The molecular basis for the malignant activity imparted by signaling of HGF/SF-Met in cancer cells has been attributed to its mitogenic and invasive properties. However, HGF/SF also induces angiogenesis, but the signaling mechanism has not been understood, nor has this activity been directly associated with HGF/SF-Met mediated tumorigenesis. HGF/SF induces expression *in vitro* of VEGF, a key agonist of tumor angiogenesis. By contrast, thrombospondin-1 (TSP-1) is a negative regulator of angiogenesis. This application discloses that, in the very same tumor cells, in addition to inducing VEGF expression, HGF/SF dramatically down regulates TSP-1 expression. TSP shut off plays an important, extrinsic role in HGF/SF-mediated tumor development, as ectopic expression of TSP-1 markedly inhibited tumor formation through the suppression of angiogenesis. While VEGF induced expression is sensitive to inhibitors of several pathways, including MAP kinase, P13 kinase and Stat3, TSP-1 shut off by HGF/SF is prevented solely by inhibiting MAP kinase activation. Thus HGF/SF is a "switch" for turning on angiogenesis. TSP-1 is a useful antagonist to tumor angiogenesis, and therefore TSP-1 and agonist peptides and mimics, as well as inducers of TSP-1, have therapeutic value when used in conjunction with inhibitors of VEGF.



— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

**(88) Date of publication of the international search report:**

30 June 2005